Remarks

Claims 1-5, 7-12, 14-19, 21 and 39-45 are pending in this application. Claims 39-45 are new. Claims 6, 13, 20 and 22-38 have been canceled without prejudice or disclaimer.

The specification, drawings and claims have been amended without adding new matter. Support to amend the specification to refer to SEQ ID NO:1 as being the precursor rather than to the mature form of EphB4 is found, *inter alia*, at the top of figure 18 where it states that the sequence is the "Homo Sapiens Ephrin type-B receptor 4 Precursor (EphB4)."

Support to amend page 7, line 28 to change "concentration" to "volume" is found, *inter alia*, on Figure 15.

In the replacement Figure 4, support to amend the units of the "x" axis of Figure 4 from mg to μg is found, *inter alia*, at specification page 28, lines 22-23. In claim 1, support for "binding" of the antibody is found, *inter alia*, at specification page 25 (line 8); and support for cells that express EphB4 is found, *inter alia*, at page 18 (lines 26-27).

In claim 5, support for the cell being a human cell is found, *inter alia*, at specification page 18 (line 20).

Support for new claims 39 and 40 is found, *inter alia*, in Figure 8 and SEQ ID NO:1. Additional support for amino acid 16 as recited in new claim 40 is found, *inter alia*, at specification page 6, line 5 and, page 9, line 4.

Support for new claims 41-45 is found, *inter alia*, at specification page 19, lines 5-7, and page 22, lines 26-28.

The Rejection under 35 U.S.C. § 112, First Paragraph (Enablement)

At Office action page 2, claims 1-5, 7-12 and 14-19 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

With regard to the evidence provided in the reply to the last Office action, US 20050084873, Examiner states that Applicant is claiming all cancer. Applicant has amended the independent claims to refer to mammalian cells and specifically to mammalian cells that express EphB4. Additionally, Applicant has added new claims 41-44 that recite specific cancers. New claim 45 is directed to an antibody that is a monoclonal antibody.

Examiner replies on White as disclosing that numerous obstacles must be overcome for successful immunotherapy, and that these include choice of target antigen, immunogenicity of the antibodies, length of half-life and ability to recruit effector functions and antibody manufacturing. However, these factors are simply generic statements. They are not specific for the methods of the invention that utilize antibodies against a specific EphB4 epitope, and they do not detract from the claimed methods for the use of the antibodies. Applicant has selected a specific target antigen. Moreover, the specification teaches that complement does not play a role in the cell death effect of the EphB4 polyclonal antibody (H-200 -Santa Cruz Biotechnology) specifically directed to

the extracellular domain amino residues 201 to 400 of EphB4 (SEQ ID NO:1). (Specification page 6, lines 16-22).

Examiner relies on Noren as stating that as recently as 2007, it was unknown if EphB4 therapeutic would be effective in the treatment of cancer. However, Applicant has discovered such a method. Applicant has discovered an EphB4 epitope and produced antibodies thereto and demonstrated that such can be effective in the treatment of cancer. There is no evidence that Noren knew of Applicant's invention because Noren does not speak with specificity to Applicant's invention. Therefore, Noren does not detract from the enablement of Applicant's invention.

Examiner relies on Bodey as stating that the employment of mAbs in the treatment of human cancer is still in its infancy. However, even assuming that statement is still correct, that statement alone does not detract from any of the teachings of the instant specification.

Examiner states that antibodies that are presently being used in cancer trials are primarily monoclonal antibodies. Also, here, even assuming that statement is still correct, that statement alone does not detract from any of the teachings of the instant specification.

Submitted herewith is a declaration under 37 C.F.R. § 1.132 by the inventor, providing *in vivo* data, as further evidence of the enablement of the teaching of the specification. Dr. Stephenson first provides *in vivo* evidence of efficacy against breast cancer. Then, Dr. Stephenson discusses how the teachings of the specification allow the artisan of ordinary skill to practice the invention against other types of cancers that involve cancerous cell that expresses EphB4 without undue experimentation.

In Vivo Studies Against Breast Cancer

In the declaration, Dr. Stephenson states that an *in vivo* study was commissioned to determine the efficacy of the novel antibodies against the MDS-MB231 Breast Tumour in Female BALB/c Nude Mice. The study was performed for the assignee by *vivo*Pharm Pty Ltd, Level 9, 195 North Terrace, Adelaide, SA 5000 Australia.

Dr. Stephenson states an antibody was raised against an epitope within residues 220 to 230 of the human EphB4 protein. The antibody produced was a mouse monoclonal antibody produced according to standard techniques in the art. The antibody was designated AB-1 (C2).

Dr. Stephenson states that the efficacy of the AB-1 (C2) antibody preparation was assessed against the human MDA-MB231 breast tumour growing as subcutaneous xenografts in female BALB/c *nu/nu* mice. The effect of the antibody preparation was compared with that of the reference therapy, Doxorubicin™ and Vehicle only control.

Dr. Stephenson states that to establish tumors, mice were inoculated with 100 μL of cells ($1x10^7$ cells) injected into the subcutaneous space just below the animal's right shoulder. Thirty female BALB/c *nu/nu* mice that developed tumours from the subcutaneously inoculated MDA-MB231 cells were selected for the study. The mice had an age range of 10-12 weeks and weight range 18.90-23.55g (mean 21.51g) at onset of treatment and were randomly divided in to 3 study groups (2 test and 1 control). Each animal was identified by a transponder (Bar Code Data Systems, Botany Bay, NSW, Australia) that was scanned with a barcode reader (DataMars LabMax I). The

transponder was implanted by subcutaneous injection between the shoulder blades while the mouse was under isofluorane-induced anaesthesia.

Dr. Stephenson states that the animals were kept in a controlled environment (targeted ranges: temperature 21±3°C, humidity 30-70%, 10-15 air changes per hour), with a light/dark cycle each of 12 hours, and under barrier (quarantine) conditions. Temperature and relative humidity were monitored continuously. All animals were subjected to the same environmental conditions and standard diet.

Dr. Stephenson states that the treatment of mice began eight days after MDA-MB231 cell inoculation, when the average tumour volume was 163 mm^3 (average variability of 4.7%).

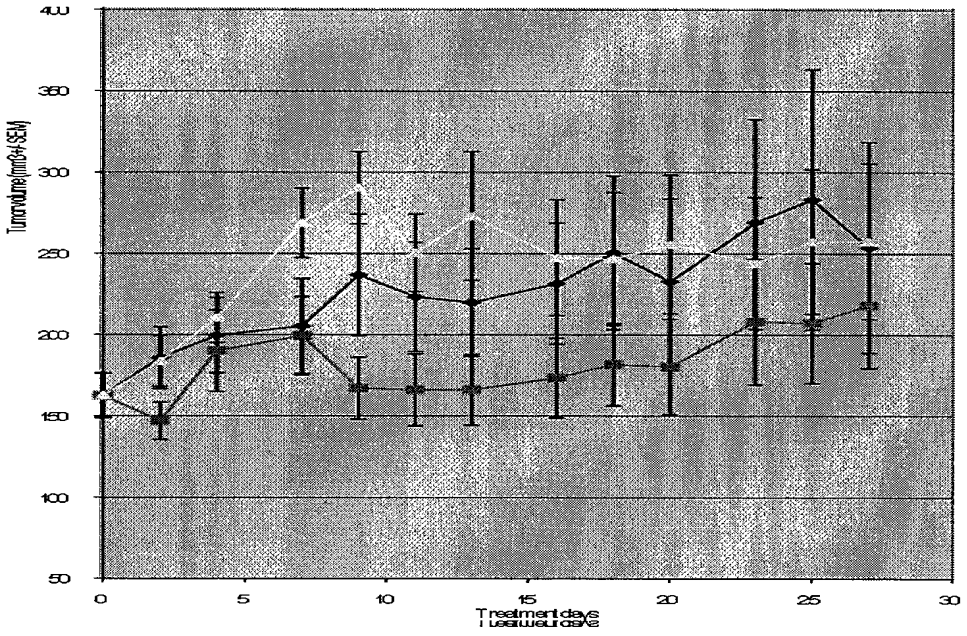
Dr. Stephenson states the groups were treated with either the Vehicle Control (Phosphate Buffered Saline), AB-1 (C2) (50 mg/kg in sterile PBS) or Doxorubicin™ (1.91 mg/kg in sterile saline). The Vehicle Control and AB-1 (C2) were each administered three times per week by intraperitoneal (i.p.) injection. Doxorubicin™ was administered three times per week by intravenous (i.v.) injection, via the tail vein. Body weight and tumour size measurements were recorded for all animals three times per week, beginning on Day 0, and including the termination day (Day 27). Adverse clinical signs were not associated with the treatments. All groups gained significant mean body weight during the study period.

Dr. Stephenson states that FIG. 1 (reproduced herein below) shows the full tumour size dataset for all study groups monitored during the course of the in vivo anticancer experiment. The black diamond shaped points are for the Vehicle Control

group (PBS), tan square points are for the AB-1 (C2) group while the lightly shaded triangle shaped points are for the Doxorubicin™ group.

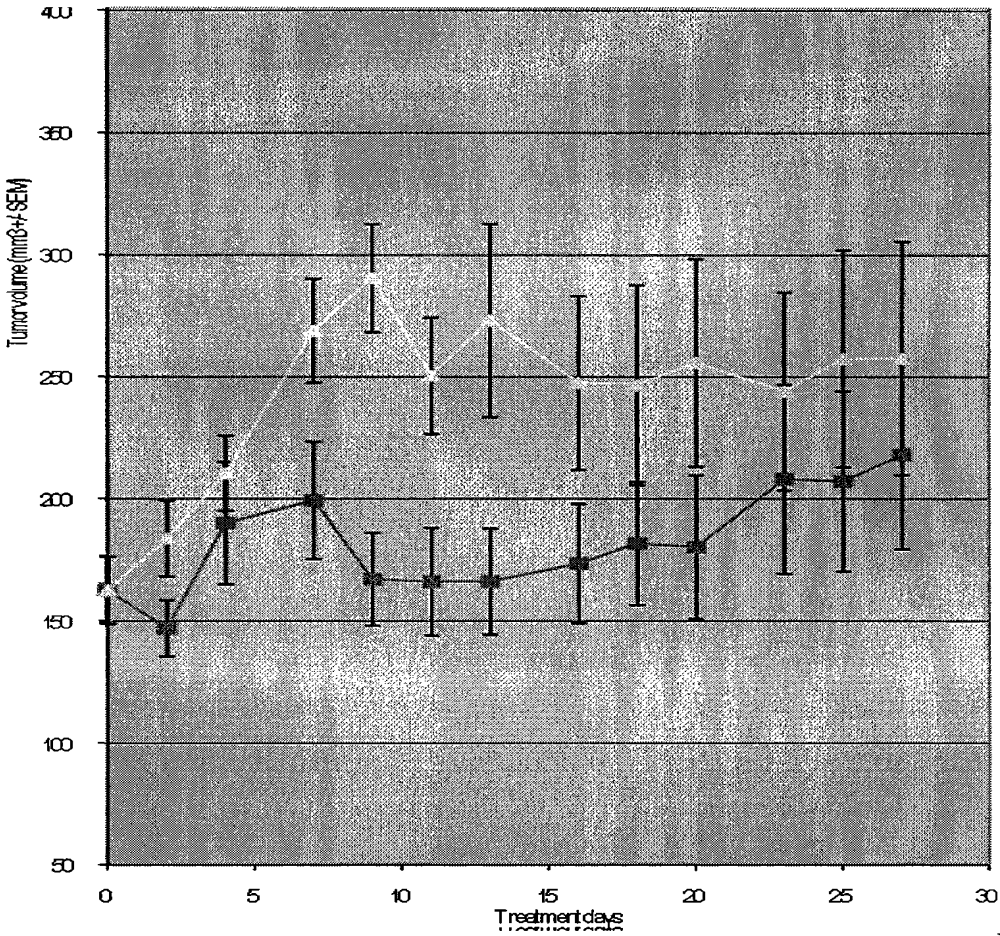
In Figure 1, below, the y axis tumour volume in mm^3. The x axis is treatment in days.

FIGURE 1



Dr. Stephenson states that FIG. 2 (reproduced herein below) shows the tumor growth data shown in FIG. 1 excluding the Vehicle Control data. The darker square points are for the AB-1 (C2) group while the lightly shaded triangle shaped points are for the Doxorubicin™ group. In Figure 2, below, the y axis tumour volume in mm^3. The x axis is treatment in days.

FIGURE 2

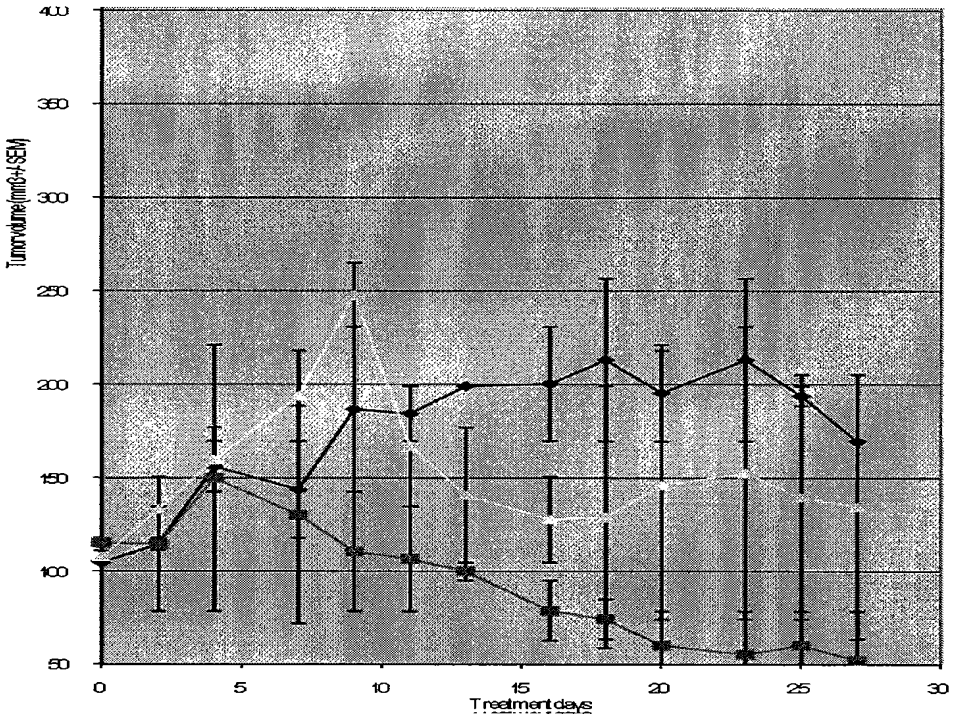


Dr.

Dr. Stephenson states that FIG. 3 (reproduced herein below) shows the tumour growth data for the two smallest starting tumours in each of the study groups. The dark diamond shaped points are for the Vehicle Control group (PBS), the tan square points are for the AB-1 group (anti-EphB4 antibody) while the lightly shaded triangle shaped points are for the Doxorubicin™ group.

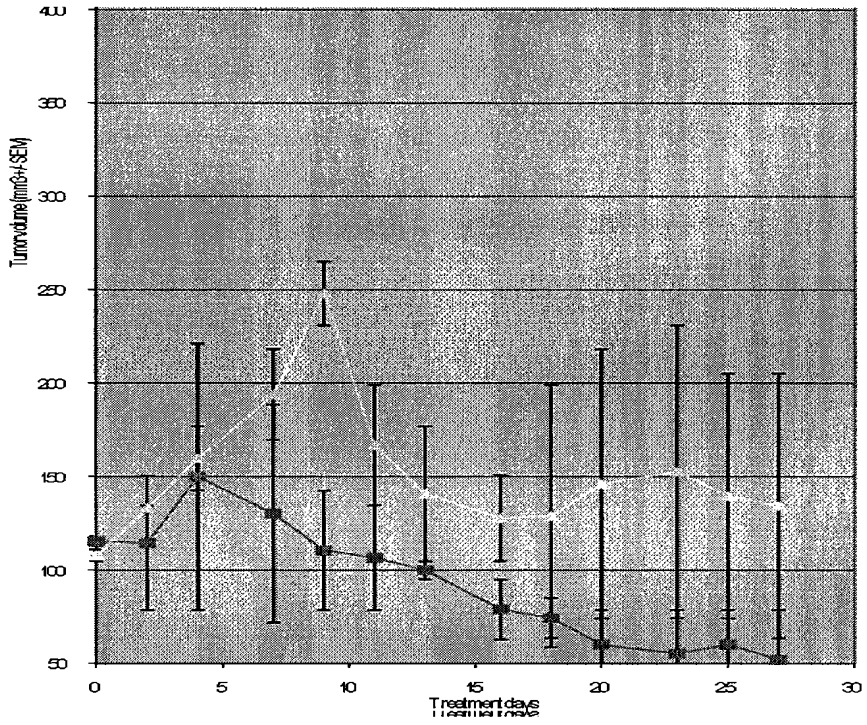
In Figure 3, the y axis tumour volume in mm^3. The x axis is treatment in days.

FIGURE 3



Dr. Stephenson states that FIG. 4 (reproduced herein below) shows the tumour growth data shown in FIG. 3 excluding the Vehicle Control data. The darker square points are for the AB-1 (C2) group while the lightly shaded triangle shaped points are for the Doxorubicin™ group. In Figure 4, the y axis tumour volume in mm^3. The x axis is treatment in days.

FIGURE 4



Dr. Stephenson states that, as shown in FIG. 1 to FIG. 4, tumour growth inhibition (measured by tumour volume) achieved following treatment with AB-1 (C2) was demonstrated to be superior to that achieved with Doxorubicin™.

Dr. Stephenson states that as can be seen in FIG. 1 and FIG. 3, growth of the tumours in the Vehicle Control group was slower than anticipated. Importantly, however, tumour growth patterns observed with Doxorubicin™ treatment were consistent with previous studies using the MDA-MB231 tumour model at this dose. In contrast, the

tumour growth patterns observed in the Vehicle Control group were not consistent with previous studies using the MDA-MB231 tumour model, suggesting that growth of tumours in the Vehicle Control group was compromised. As such, FIG. 2 and FIG. 4 show the data from FIG. 1 and FIG. 3, respectively, with the Vehicle Control group data excluded.

Dr. Stephenson concludes that, in brief summary, thirty female BALB/c *nu/nu* mice, which developed tumours from subcutaneously inoculated MDA-MB231 cells (1×10^7 cells/mouse), were selected for the study. The mice were implanted with a uniquely identified microchip and randomised into three treatment groups of ten mice each. The allocation of mice was such that each group had similar mean starting tumour volumes of approximately 163 mm^3 with a variability of 4.7%.

Dr. Stephenson summarizes that the groups were treated with either Vehicle Control, Phosphate Buffered Saline (PBS), AB-1 (C2) (50 mg/kg) or Doxorubicin™ (1.91 mg/kg). The Vehicle Control and AB-1 (C2) were each administered three times per week by intraperitoneal (i.p.) injection. Doxorubicin™ was administered three times per week by intravenous (i.v.) injection, via the tail vein.

Dr. Stephenson summarizes that treatments began on Day 0. The study was initially scheduled to continue for three weeks. Due to delayed growth of the tumours in the Vehicle Control group and with the consent of the Sponsor, the treatment period was extended for an additional week.

Dr. Stephenson summarizes that body weight and tumour size measurements were recorded for all animals three times per week, beginning on Day 0, and including the termination day (Day 27).

Dr. Stephenson concludes that adverse clinical signs were not associated with the treatments. All groups gained significant mean body weight during the study period.

Dr. Stephenson concludes that tumour growth inhibition achieved following treatment with AB-1 (C2) was demonstrated to be superior to that achieved with Doxorubicin™, however, slower than anticipated growth of the tumours in the Vehicle Control group meant that definitive statistical comparison of the tumour volume data at termination could not be made. Importantly, tumour growth patterns observed with Doxorubicin™ treatment were consistent with previous *vivo*Pharm studies using the MDA-MB231 tumour model at this dose (data not shown in this report). In contrast, tumour growth patterns observed in the Vehicle Control group were not consistent with previous *vivo*Pharm studies using the MDA-MB231 tumour model (data not shown in this report) suggesting that growth of tumours in this group was compromised in some way, the cause and reasons for which are unknown.

Efficacy in Other Cancers

Dr. Stephenson states that, as noted by Examiner, the specification demonstrated that EphB4 expression is upregulated in colon and breast cancer cell, and that polyclonal antibodies to EphB4 induced cell death in breast and colon cancer cell lines.

Dr. Stephenson states that the teachings regarding breast and colon cancer cell lines can be extrapolated without undue experimentation to other cancer cells in which EphB4 expression is upregulated. Dr. Stephenson states she reaches this conclusion because it is the EphB4 epitope that is being targeted and that epitope is common to the EphB4 that is expressed by other cells in other forms of cancers in which EphB4 is

upregulated. An increased expression of EphB4 in any tumour suggests that EphB4 signal is playing a role in the development of the tumour phenotype.

Dr. Stephenson states that thus, by the specification teaching and demonstrating that cell death can be induced in tumour cells such as breast and colon cancer cell lines by targeting the epitope on EphB4 that is between amino acids 200 and 400 of SEQ ID NO:1, the specification teaches the specific target that is all that the artisan needs to know to also practice this invention against other tumour cells and cancers in which EphB4 is upregulated.

Dr. Stephenson states that the structure of EphB4 that was expressed in the breast cancer cells and colon cancer cells as demonstrated in the examples is the same as, or very similar to, the EphB4 that is expressed in other tumor types.

Dr. Stephenson states that the role or mechanism of action of EphB4 is expected to be the same in other cancer cell types that express EphB4 as it is in breast cancer cells and colon cancer cells.

Dr. Stephenson states that the effect of an antibody that is directed to an epitope between amino acids 200 and 400 of SEQ ID NO:1 would be the same in any cancer cell in which EphB4 is upregulated, including the impact of the same on inhibiting the cancerous growth of the cell, or inducing cell death, or in treating or preventing cancer that results from such cells in the subject.

Dr. Stephenson concludes that therefore, since the target is the same, and the same antibodies can be used against the those targets in a variety of cancer cell types, then the invention can be practiced without undue experimentation in cancers other than those exemplified in the examples of the specification.

***Prima facie* lack of enablement is not established**

Applicant respectfully asserts that *prima facie* lack of enablement is not established, or, if it has been established, it has been overcome.

The data presented in the accompanying declaration confirm the teachings of the specification. These data provide *in vivo* data that demonstrate the efficacy of the claimed methods. These data show that the volume of the tumour was the lower in the group that received the mouse monoclonal antibody that was raised against an epitope within residues 220 to 230 of the human EphB4 protein, than it was in the group that received Doxorubicin™.

The adequacy of the disclosure is judged from the perspective of one of ordinary skill in the art. Applicant respectfully asserts that Dr. Stephenson's Declaration clearly establishes that the specification is enabled for the claimed invention.

The purpose of the requirement that the specification describe the invention in such terms that one skilled in the art can make and use the claimed invention without undue experimentation (i.e., the enablement requirement) is to ensure that the invention is communicated to the interested public in a meaningful way. Here, Applicant respectfully asserts that the information contained in the disclosure of the specification is sufficient to inform those skilled in the relevant art how to both make and use the claimed invention in a manner that satisfies the requirements of 35 U.S.C. § 112, first paragraph for enablement.

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), aff'd. sub

nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Here Applicants respectfully assert that even if any experimentation was performed it would not be undue as it would be of the type typically engaged in by artisans in this art.

Moreover, as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

It is incumbent upon the Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Examiner has cited documents that in the Examiner's opinion provide a reason to doubt the objective truth of the statements in the specification. However, Applicant has demonstrated that such statements were generic and not specific for the claimed invention, and therefore did not detract from the

invention. Also, Applicant has provided data that demonstrate *in vivo* efficacy in an animal model.

35 U.S.C. § 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. It is not necessary that every permutation within a generally operably invention be effective in order to an inventor to obtain a generic claim, provided that that effect is sufficiently demonstrated to characterize a generic invention. See Capon v. Eshihar, 418 F.3d 1349 (Fed. Cir. 2005); In re Angstadt, 537 F.2d 498, 504 (CCPA 1976).

The amendments and discussion above, and the accompanying evidence clearly establish that *prima facie* lack of enablement is not established, or, if it has been established, it can be withdrawn.

Conclusion

Prompt and favorable consideration of this Amendment and Reply is respectfully requested. Applicant believes the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Date: March 13, 2009

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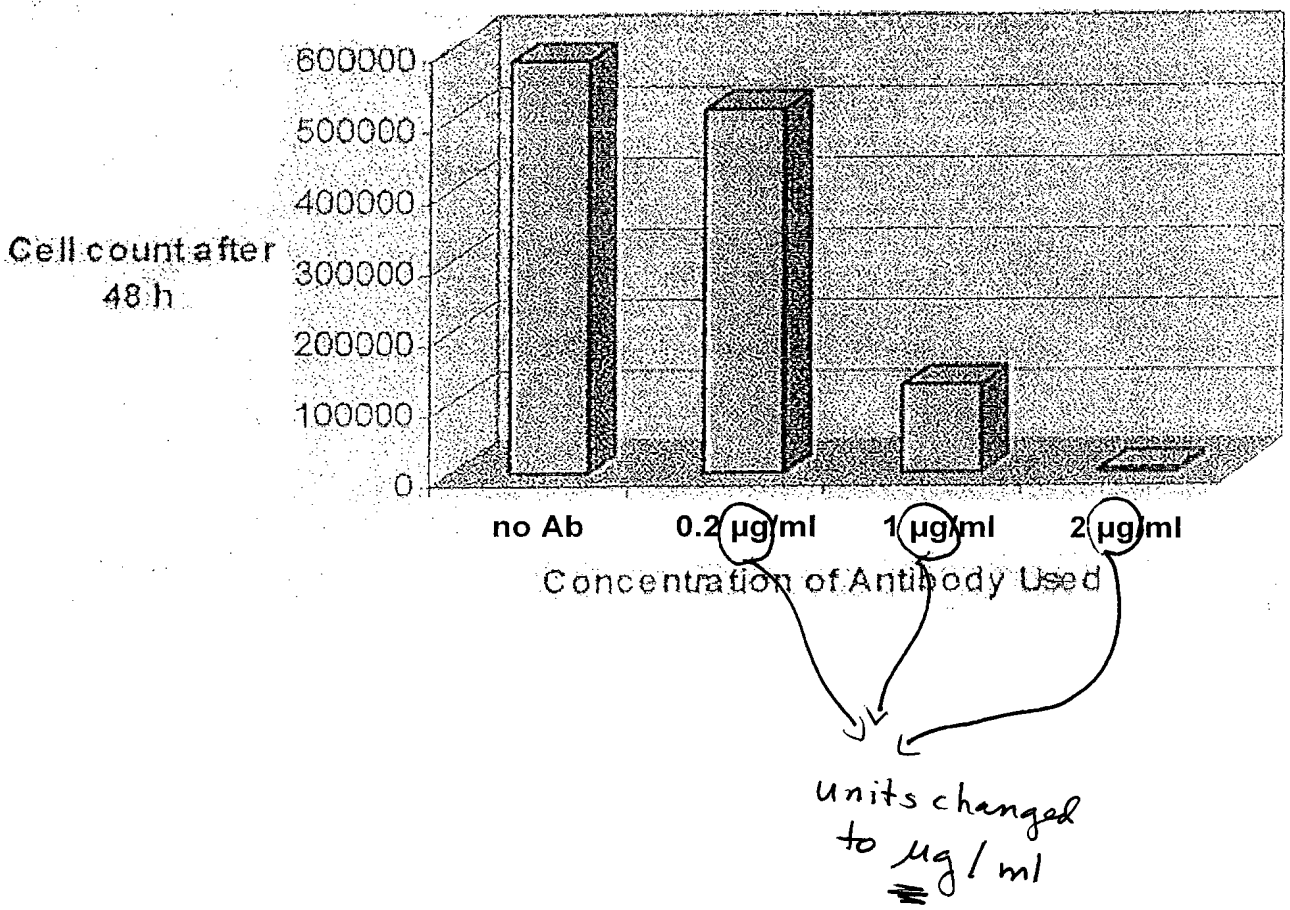
937518.1

Figure 4


600000
500000
400000
300000
200000
100000
0
Cell count after 48 h
no Ab
0.2 µg/ml
1 µg/ml
2 µg/ml
Concentration of Antibody Used
Units changed to µg/ml